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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,980	02/08/2002	Dan Gazit	P-4891-US1	9918

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,980	GAZIT ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *1-22,30-41 and 48-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-29 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/376,276.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-63 are pending in the present application.

Applicant's election of Group IV (Claims 23-29 and 42-47) in the Response to Restriction Requirement filed on 2/26/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 1-22, 30-41 and 48-63 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 23-29 and 42-47 are examined on the merits herein.

Priority

The present application is a continuation-in-part of U.S. Serial No. 09/376,276, filed August 18, 1999, now abandoned, which claims foreign priority of the German application, filed August 18, 1998.

Upon review of the specifications of the parent (U.S. Serial No. 09/376,276) and the German applications and comparison with the specification of the present application, it is determined that the pending and examined claims are only entitled to the priority benefit of the filing date of February 08, 2002. This is because the method of repairing or forming a cartilage in a subject in need and the composition as claimed are not supported by the specifications of the parent US and German applications.

Accordingly, claims 202-205 are only entitled to the priority benefit of the filing date of January 30, 1996 for the reasons set forth above.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because of the absence of signatures by all other inventors except Stefan Czichos.

Sequence Compliance

The specification contains nucleotide sequences and amino acid sequences that have not been assigned with SEQ ID NOs in either a paper sequence listing or in a CRF (see page 21, top of first paragraph; page 22, last line continues to the first paragraph of page 23). **Failure to comply with the sequence rules will be deemed as non-responsive in the reply of this Office Action.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-29 and 42-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1. A method of repairing or forming a cartilage in a subject in need comprising the steps of:

a. obtaining a mesenchymal stem cell from the subject,

b. transfecting said cell with a recombinant vector comprising a nucleic acid sequence encoding Brachyury, so as to obtain an engineered mesenchymal stem cell which expresses Brachyury; and

c. administering said engineered mesenchymal stem cell to a site of cartilage damage in the subject, and thereby repairing or forming a cartilage in the subject;

2. A composition comprising an engineered mesenchymal stem cell which expresses Brachyury and a pharmaceutically acceptable carrier;

does not reasonably provide enablement for a method of repairing or forming a cartilage in a subject in need by administering any engineered cell expressing any factor of the T-box family to the subject at any site; and a composition comprising any engineered cell which expresses any factor of the T-box family and a pharmaceutically acceptable carrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 23-29 are directed to a method of repairing or forming a cartilage in a subject in need thereof comprising the steps of: obtaining a cell from the subject; transfecting said cell with a recombinant vector comprising a nucleic acid sequence encoding a factor of the T-box family, so as to obtain an engineered cell which expresses a factor of the T-box family; and administering said engineered cell to the subject. Claims 42-47 are drawn to a composition comprising an engineered cell which expresses a factor of the T-box family and a pharmaceutically acceptable carrier.

With respect to the nature of the elected invention, the specification teaches by exemplification showing that forced expression of Brachyury, a member of the T-box family, in embryonic mouse mesenchymal C3H10T1/2 stem cells gave rise to efficient chondrogenic differentiation *in vitro*; and ectopic transplantation of these genetically engineered cells in murine intramuscular sites results in massive formation of proliferating chondrocytes and cartilage (see example 2).

The above evidence has been noted and considered. However, the instant specification is not enabled for the instant broadly claimed invention for the following reasons. With respect to claims 42-47, when read in light of the instant specification the sole purpose for the claimed composition is for enhancing repair of a cartilage and/or inducing formation of a cartilage (see page 1, paragraph 0001).

1. The breadth of the claims

The claims are drawn to a method of repairing or forming a cartilage in any subject in need comprising the steps of: obtaining any cell from the subject, transfecting said cell with a recombinant vector comprising a nucleic acid sequence encoding any

factor of the T-box family, and then administering the genetically modified cell to the subject at any site; and a composition comprising any engineered cell which expresses any factor of the T-box family and a pharmaceutically acceptable carrier.

2. The state and the unpredictability of the prior art

At about the effective filing date of the present application (2/8/2002), virtually nothing was known on the use of any cell genetically engineered with any member of the T-box transcriptional family in a therapeutic application for cartilage repair or formation (Hoffmann et al., J. Cell Science 115:769-781, 2002; Gafni et al. Gene therapy 11:417-426, 2004). Cartilage is a tissue known for its difficulty in self-repair due to its poor vascularization, insufficient stem cell recruitment as well as persistent chronic inflammation under rheumatoid arthritic conditions.

T-box genes are DNA-binding transcriptional factors that play diverse roles in metazoan embryonic development, in the differentiation of all three embryonic germ layers and in organognesis (Papaioannou et al., BioEssays 20:9-19, 1998; Smith, J. TIG 15:154-158, 1999). There are at least five interrelated T-box subfamilies: T, Tbx1, Tbx2, Tbx6 and Tbr1, and at about the effective filing date of the present application there is still a need to understand how expression of these T-box genes are regulated, to identify their targets and to understand how different family members exert different effects.

3. The amount of direction or guidance provided

Apart from the exemplification showing that forced expression of Brachyury in mouse embryonic mesenchymal C3H10T1/2 stem cells gave rise to efficient

chondrogenic differentiation *in vitro*; and ectopic transplantation of these genetically engineered cells in murine intramuscular sites results in massive formation of proliferating chondrocytes and cartilage, the instant specification fails to provide sufficient guidance for a skilled artisan on how to use any other Brachyury transfected cell types for repairing or for forming cartilage in a subject in need thereof. It is not clear whether Brachyury could exert the same effects (e.g., proliferation and chondrogenic differentiation) on cell types other than mesenchymal stem cells as those obtained for mouse embryonic mesenchymal stem cells to yield the desired therapeutic effects. It should be noted that Brachyury contains multifunctional domains and its *in vivo* function seems to require the interaction of accessory factors with its transactivation and/or repression domains. Additionally, the instant specification fails to provide sufficient guidance for a skilled artisan on how to use any other members of the T-box family for repairing or for forming a cartilage in a subject in need thereof. At the effective filing date of the present application, there was still a need to understand how different family members of the T-box gene family exert different effects as well as to identify their target genes. Therefore, it is uncertain whether other members of the T-box family bind to the same or different DNA sequences, with the same or different affinities, to regulate the same set or different set of target genes as Brachyury to yield the same effects observed for mouse embryonic mesenchymal stem cells, let alone for any cell types obtained from the patient in need of treatment. In other words, there is no evidence of record indicating that other T-box gene members can substitute for Brachyury to yield the therapeutic effects desired by Applicants. Even two years after the filing date of the

present application, some of the present Applicants still state that "[w]e have characterized a novel transcription factor from the T-box family (Brachyury) that induces chondrogenic differentiation **only in MSCs**" (Gafni et al., page 422, col. 2, top of last paragraph). Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so.

The physiological art is recognized as unpredictable (MPEP 2164.03). Given the state of the prior art as already discussed above, coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the method and composition as claimed.

Furthermore, with respect to the method claims the instant specification fails to provide sufficient guidance for a skilled artisan on how to repair or forming a cartilage in a subject in need by administering the engineered cell at any site to the subject. There is no evidence of record indicating that any genetically modified cell of the presently claimed invention is capable of targeting to any site in need of repairing or forming a cartilage in a subject. Once again, since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the instant specification to do so. With the lack of sufficient guidance provided by this disclosure, it would have required undue experimentation for a skilled artisan to make and use the method as broadly claimed.

4. The quantity of experimentation provided

Apart from the exemplification showing that forced expression of Brachyuryin embryonic mouse mesenchymal C3H10T1/2 stem cells gave rise to efficient chondrogenic differentiation *in vitro*; and ectopic transplantation of these genetically engineered cells in murine intramuscular sites results in massive formation of proliferating chondrocytes and cartilage, the instant specification fails to provide any other examples showing that other members of a large T-box family are also effective in inducing chondrogenic differentiation in mesenchymal stem cells *in vitro* and/or *in vivo*. Nor does the instant disclosure provide any other examples showing that Brachyury is also effective in inducing chondrogenic differentiation in any other cell types in either *in vitro* or *in vivo* to yield the therapeutic effects contemplated by Applicants.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the relevant art on cells genetically modified with a factor of the T-box transcriptional factor family to repair or forming a cartilage in a subject in need, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 23 and its dependent claims, there is no linkage between the recited steps with the preamble "repairing or forming a cartilage" of the claims. Therefore, the metes and bounds of the claims are not clearly determined.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 23-29 and 42-47 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 23-29 and 43-48 of copending Application No. 10/298215. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER